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ARTICLE

Aspirin, Nonaspirin Nonsteroidal Anti-inflammatory Drug, and Acetaminophen Use and Risk of Invasive Epithelial Ovarian Cancer: A Pooled Analysis in the Ovarian Cancer Association Consortium

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Background Regular aspirin use is associated with reduced risk of several malignancies. Epidemiologic studies analyzing aspirin, nonaspirin nonsteroidal anti-inflammatory drug (NSAID), and acetaminophen use and ovarian cancer risk have been inconclusive.

Methods We analyzed pooled data from 12 population-based case–control studies of ovarian cancer, including 7776 case patients and 11 843 control subjects accrued between 1992 and 2007. Odds ratios (ORs) for associations of medication use with invasive epithelial ovarian cancer were estimated in individual studies using logistic regression and combined using random effects meta-analysis. Associations between frequency, dose, and duration of analgesic use and risk of ovarian cancer were also assessed. All statistical tests were two-sided.

Results Aspirin use was associated with a reduced risk of ovarian cancer (OR = 0.91; 95% confidence interval [CI] = 0.84 to 0.99). Results were similar but not statistically significant for nonaspirin NSAIDs, and there was no association with acetaminophen. In seven studies with frequency data, the reduced risk was strongest among daily aspirin users (OR = 0.80; 95% CI = 0.67 to 0.96). In three studies with dose information, the reduced risk was strongest among users of low dose (<100 mg) aspirin (OR = 0.66; 95% CI = 0.53 to 0.83), whereas for nonaspirin NSAIDs, the reduced risk was strongest for high dose (≥500 mg) usage (OR = 0.76; 95% CI = 0.64 to 0.91).

Conclusions Aspirin use was associated with a reduced risk of ovarian cancer, especially among daily users of low-dose aspirin. These findings suggest that the same aspirin regimen proven to protect against cardiovascular events and several cancers could reduce the risk of ovarian cancer 20% to 34% depending on frequency and dose of use.

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Ovarian cancer is the most fatal gynecologic malignancy, causing more than 140 000 deaths each year worldwide (1). Although early stage ovarian cancer can be successfully treated, the disease is commonly detected at advanced stages with extensive local and systemic spread and poor survival. Early detection strategies have not been shown to reduce mortality (2,3), and biomarker candidates have had insufficient performance to improve early detection efforts thus far (4,5). Primary prevention strategies have not been widely studied but may present alternatives to reduce ovarian cancer burden.

Multiple lines of evidence suggest that ovarian cancer may be related to chronic inflammation (6). In addition to inflammatory factors associated with ovarian epithelial disruption through ovulation (7–9), inflammation-related exposures such as endometriosis (10–12) and exposure to talc or genital powder and asbestos (13) have been associated with increased ovarian cancer risk.

Recently, intervention trials have shown that regular aspirin use is associated with reduced risk of several malignancies (14). However, these trials were not powered for rare cancer endpoints, and none of the clinical trials to date have evaluated ovarian cancer separately. Recent meta-analyses of aspirin use have reached various conclusions that range from no effect (15) to a weak risk reduction among regular users of aspirin (16–18). For nonsteroidal

anti-inflammatory drug (NSAID) use, a recent summary suggested a greater risk reduction among cohort studies than among case–control studies (15), whereas, the results from individual epidemiologic studies have been largely inconclusive (13,19–33), possibly because of limited sample size and limited data on dose, duration, and frequency of use across the studies.

We conducted an analysis of pooled individual-level data of NSAID use and ovarian cancer risk in the Ovarian Cancer Association Consortium (OCAC), including more than 7500 ovarian cancer cases from 12 population-based case–control studies.

Methods

Study Population

We analyzed individual-level data from 12 population-based case–control studies participating in OCAC that had available data on aspirin, nonaspirin NSAID, or acetaminophen (paracetamol) use. All studies had approval from ethics committees, and written informed consent was obtained from study participants. Data acquisition and data pooling for each study were approved by the institutional review board or research ethics committees of the institutes sponsoring the study.

The 12 studies were as follows: the Australian Ovarian Cancer Study and Australian Cancer Study (26), the Connecticut Ovarian Cancer Study (34), the Diseases of the Ovary and their Evaluation Study (23,35), the Hawaii Ovarian Cancer Case–Control Study (36,37), the Hormones and Ovarian Cancer Prediction Study (38), the Malignant Ovarian Cancer Study (39), the North Carolina Ovarian Cancer Study (40,41), the New England Case–Control Study of Ovarian Cancer (42), the New Jersey Ovarian Cancer Study (43), the University of California, Irvine Ovarian Cancer Study (44), the United Kingdom Ovarian Cancer Population Study (45), and the University of Southern California Study of Lifestyle and Women's Health (13) (Table 1). In total, the study included data from nine case–control studies conducted in the United States (13,23,34,37,38,40,42–44), one study conducted in Denmark (39), one study conducted in the United Kingdom (45), and one study conducted in Australia (26).

From these 12 studies, 10 161 ovarian cancer case patients and 12 382 control subjects were available for the analysis. For the primary analysis, we excluded case patients whose cancers were nonepithelial (n = 43), of low malignant potential (n = 2059), or missing data on both the malignant potential of the tumor and tumor grade (n = 68). We further excluded study participants with missing data for all three exposure variables (n = 215 case patients and n=539 control subjects), leaving 7776 invasive ovarian cancer case patients and 11 843 control subjects for our analysis. The case patients were divided into four categories by the four main histologic subtypes of the cancer: serous (n = 4510), endometrioid (n = 1163), clear cell (n = 677), and mucinous (n = 423). The remaining 1003 case patients with cancers of other histologic type were not included in subtype analyses. We also evaluated associations for high-grade serous ovarian tumors (grade II–IV; n = 3786) based on the prevailing view that high-grade serous tumors are distinct from low-grade (grade I; n = 330) serous tumors (46). We evaluated 2059 case patients with cancers of low malignant potential in a separate analysis.

Study Variables

Data for medication use was self-reported in all studies (Table 1). Ten of the 12 studies asked about "regular use" of medications over a specified time period with a minimum frequency of use (13,23,34,38–40,42–45). The duration of regular use varied in the 10 studies, from 1 month to 1 year of use. The majority of the studies, six of 10, specified 6 months or more as the minimum duration (23,38,42–45). The definition for frequency of regular use also varied by study, ranging from once per week to daily; the majority of the studies (n = 8 of 10) specified once or twice per week as the minimum frequency of regular use (13,23,34,38,39,42,44,45). The two remaining studies did not specify regular use, so we reclassified study participants as regular users if their reported frequency of use was at least once per week (26) or if their frequency of use was at least five pills per month and their duration of use was at least 6 months (37).

The exposures used in this analysis were regular (at least once per week) use of aspirin, nonaspirin NSAIDs, and acetaminophen and nonregular use (reference group; less than once a week use for each category). Data for nonaspirin NSAID use were provided in all studies except for two studies that combined aspirin use with other NSAIDs (44,45). Medication use was further classified by frequency [<30 days per month and daily; n = 7 studies (13,23,26,37-40)], dose [<100 and ≥100 mg for aspirin to differentiate between use of low- and regular/high-dose formulations; <500 mg and ≥ 500 mg for non-aspirin NSAID and acetaminophen to differentiate between standard and high-dose formulations; n = studies (37,38,40)], and duration [<60 months and ≥60 months; n = 8 studies (13,23,34,37-39,42,43)] of use based on available data from the individual studies. We created a frequency–dose combination exposure variable based on cross-tabulations of the original categorical variables [(n = 3 studies) (37,38,40)].

Potential confounding variables were available from all studies as part of a core dataset and were harmonized by the coordinating center. Continuous variables were categorized in all analyses for ease of interpretation and to reduce the effect of any outliers. Variables that were selected a priori as adjustment factors included age (5-year categories), race (white, black, other), body mass index (<25, 25–29, ≥30 kg/m^2), use of oral contraceptives (ever, never), parity (nulliparous, 1 full-term birth, >1 full-term birth), menopausal status (pre- or postmenopausal based on study-specific algorithm), and family history of breast or ovarian cancer in a first-degree relative (defined as any breast or ovarian cancer reported in mother, sister, or daughter or breast cancer reported in father). Potential confounding was also evaluated, but not found, for the following variables: Hispanic ethnicity, history of breast feeding, use of estrogen menopausal hormone therapy, use of estrogen plus progestin menopausal hormone therapy, tubal ligation, hysterectomy, and history of endometriosis.

Statistical Analyses

We used multivariable logistic regression models to estimate study-specific odds ratios (ORs) and 95% confidence intervals (CIs) for the association between NSAID exposure and ovarian cancer risk. Study-specific odds ratios were pooled using random-effects meta-analysis to generate a summary odds ratio. For the analyses of the primary exposures (regular use, dose, duration, and frequency), two

Table 1. Characteristics of population-based case–control studies from the Ovarian Cancer Association Consortium included in the pooled analysis*

Study	OCAC acronym	Location	Ascertainment period	Study subjects: Case patients (n = 7776)	Study subjects: Control subjects (n = 11 843)	Question pertaining to drug use	Prevalence of exposure in control subjects: Aspirin %	Nonaspirin NSAID‡ %	Acetaminophen %
Australian Ovarian Cancer Study & Australian Cancer Study† (26)	AUS	Australia	2002–2005	1311	1505	How often have you taken the following over-the-counter (aspirin, paracetamol, anti-inflammatory drugs) medications during PAST 5 years?	10	16	25
Connecticut Ovarian Cancer Study (34)	CON	USA	1999–2003	388	551	Have you ever taken any of the medications shown on this card regularly (at least once per week on average over a duration of 3 months or more)?	26	28	16
Diseases of the Ovary and their Evaluation Study (23,35)	DOV	USA	2002–2009	1159	1849	Before reference date have you taken any of these medications (show card) 5 or more days per month for at least 6 months?	22	27	16
Hawaii Ovarian Cancer Case–Control Study (36,37)	HAW	USA	2001–2008	256	485	Did you ever take an aspirin product (show card) at least 12 times a year? Identical questions ascertained use of acetaminophen (aspirin-free) and NSAIDs.	26	25	22
Hormones and Ovarian Cancer Prediction Study (38)	HOP	USA	2003–2008	683	1513	Prior to reference date have you ever used aspirin (show card) for at least two tablets per week continuously for a period of 6 months or longer? Identical questions ascertained use of over-the-counter pain or inflammation reliever other than aspirin.	34	33	19
Malignant Ovarian Cancer Study (39)	MAL	Denmark	1994–1999	554	1564	Did you ever take medicine on a regular basis, i.e. two times or more per week for more than one month for any of the following conditions?	8	9	5
North Carolina Ovarian Cancer Study (40,41)	NCO	USA	1999–2008	939	1085	For the 5 years prior to diagnosis, did you take any of these over-the-counter medications (show card) on a regular basis for at least 3 months?	11	38	20
New England Case–Control Study of Ovarian Cancer (42)	NEC	USA	1992–2003	870	1243	Prior to reference date have you ever used any over-the-counter pain reliever (show card) continuously at least once a week for a period of 6 months or longer?	18	25	22

(Table continues)

Table 1 (*Continued*).

Study	OCAC acronym	Location	Ascertainment period	Study subjects: Case patients (n = 7776)	Study subjects: Control subjects (n = 11 843)	Question pertaining to drug use	Prevalence of exposure in control subjects: Aspirin %	Nonaspirin NSAID‡ %	Acetaminophen %
New Jersey Ovarian Cancer Study (43)	NJO	USA	2002–2008	238	458	Prior to reference date did you ever take any over-the-counter medications continuously for 6 months or longer (this includes prescriptions, over-the-counter medications, and any natural or alternative treatments you may have taken).	16	9	3
University of California, Irvine Ovarian Cancer Study (44)	UCI	USA	1995–2005	393	313	Have you taken medication listed (aspirin, ibuprofen, acetaminophen, naproxen) regularly? By regular, we are referring to use of the drug or medication at least once a week for a year, or more than 50 pills during a one year-period.	26	41‡	17
United Kingdom Ovarian Cancer Population Study (45)	UKO	UK	2006–2007	516	598	Have you ever used any medication containing the drugs (aspirin, ibuprofen) on a regular basis (by regular we mean every day or almost every day for 6 months or longer)?	15	16‡	—
University of Southern California Study of Lifestyle and Women's Health (13)	USC	USA	2000–2005	469	679	Before reference date, as an adult, did you ever take any prescription or non-prescription medicine at least 2 or more times per week for one month or longer?	15	16	13
						Overall	18	24	16

* NSAID = nonsteroidal antiinflammatory drug; OCAC = Ovarian Cancer Association Consortium.

† Combined for the purpose of this analysis.

‡ UCI and UKO reported data on NSAIDs, including aspirin; the remaining studies provided data on nonaspirin NSAIDs.

multivariable logistic regression models were used: 1) a minimally adjusted model that included covariables for age and race and 2) a fully adjusted model that included age, race, body mass index, oral contraceptive use, parity, menopausal status, and family history of breast or ovarian cancer in a first-degree relative. The summary odds ratios from the fully adjusted model were attenuated slightly compared with the minimally adjusted model. We present the results from the fully adjusted model. We further evaluated models stratified by age (<55 and ≥55 years old), body mass index (<25 and ≥25 kg/m²), oral contraceptive use (ever/never), and history of endometriosis (yes/no). We assessed asymmetry in study estimates using a funnel plot, and when data were sufficient (n > 5 studies), we formally assessed asymmetry using the adjusted rank correlation (47) and regression asymmetry tests (48). Interstudy heterogeneity was evaluated using I^2.

The following sensitivity analyses were performed: 1) exclusion of tubal or primary peritoneal cases (n = 461); 2) restriction to white non-Hispanic participants because 85% of the participants were of white race and non-Hispanic ethnicity; 3) use of a common reference group analysis, coding "nonregular users" as women who reported no regular use of aspirin or nonaspirin NSAIDs or acetaminophen; 4) restriction of pooled analysis to the six studies that specified 6 months or more as the minimum duration; 5) restriction of pooled analysis to the nine US studies; and 6) exclusion from the pooled analysis the two studies (23,45) with the most restrictive definition of medication use given concerns for misclassification of regular users as unexposed. All statistical tests were two-sided, and P values less than .05 were considered statistically significant. All analyses were performed using STATA software version 11.2 (StataCorp LP, College Station, TX).

Results

Study site, number of case patients and control subjects, and exposure prevalence for each of the 12 OCAC studies are described in Table 1. Overall, 18% of the study population reported regular use (at least once per week) of aspirin, 24% reported regular use of nonaspirin NSAIDs, and 16% reported regular use of acetaminophen.

Aspirin

Figure 1A shows the association between aspirin use (regular vs nonregular use) and ovarian cancer risk. Regular aspirin use was associated with a reduced risk of ovarian cancer (OR = 0.91; 95% CI = 0.84 to 0.99; I^2 = 5.2%). Among seven studies that reported information on frequency of use, daily use was associated with a 20% reduction in ovarian cancer risk (OR = 0.80; 95% CI = 0.67 to 0.96) (Table 2). Among three studies that reported information on dose, low-dose aspirin use (<100 mg/day) was associated with a 34% reduction in ovarian cancer risk (OR = 0.66; 95% CI = 0.53 to 0.83) (Table 2). In analyses of combined categories of frequency and dose of aspirin use, the reduced risk was apparent for daily users of aspirin regardless of dose (low dose: OR = 0.64, 95% CI = 0.50 to 0.81; high dose: OR = 0.78, 95% CI = 0.62 to 0.97) (Table 3).

In subtype analyses, regular aspirin use was associated with reduced risks of serous, endometrioid, and mucinous ovarian cancer, but only the results for serous cancer reached statistical significance (OR = 0.89; 95% CI = 0.80 to 0.99) (Table 4). Pairwise comparisons showed no significant differences in risk between the subtypes (P > .05).

Nonaspirin NSAIDs

Regular nonaspirin NSAID use was associated with a reduced, albeit not statistically significant, risk of ovarian cancer (OR = 0.90; 95% CI = 0.77 to 1.05; I^2 = 73.2%) (Figure 1B). Among the three studies that reported information on dose, high-dose nonaspirin NSAID use (≥500 mg/day) was associated with a 24% reduction in ovarian cancer risk (OR = 0.76; 95% CI = 0.64 to 0.91) (Table 2). In analyses of combined categories of frequency and dose, the reduced risk of ovarian cancer was apparent among both categories of high-dose nonaspirin NSAID use (<30 days per month: OR = 0.77, 95% CI = 0.57 to 1.04; daily: OR = 0.75; 95% CI = 0.60 to 0.94), with a weaker association with daily users of low-dose nonaspirin NSAIDs (OR = 0.88; 95% CI = 0.70 to 1.11) (Table 3). The association between nonaspirin NSAIDs and risk was strongest for serous cancers but did not differ across histologic subtypes of ovarian cancer (Table 4).

Acetaminophen

Acetaminophen use was not associated with ovarian cancer risk (OR = 0.99; 95% CI = 0.88 to 1.12; I^2: 40.0%) (Figure 1C). No associations were observed when analyzing dose, duration, or frequency of acetaminophen use and ovarian cancer risk (Table 2). Further we observed no association between acetaminophen use and histologic subtypes of ovarian cancer (Table 4).

Additional Analyses

The association between NSAID use and high-grade serous tumors was not substantially different than the results reported for all serous tumors combined (results not shown). Tumors of low malignant potential (n = 2059) were not associated with analgesic use (data not shown). In analyses stratified by age, body mass index, oral contraception use, and history of endometriosis, similar NSAID use and ovarian cancer associations were observed as in the overall population (results not shown). Based on the adjusted rank correlation and regression asymmetry tests, there was no indication of small study effects (all P > .05) in the summary estimates for the associations between regular use of aspirin, nonaspirin NSAIDs, or acetaminophen and ovarian cancer. Although there was heterogeneity in the definition of nonaspirin NSAID use, individual exclusion of each study did not substantially change the summary odds ratio (results not shown); however, the exclusion of two studies (13,44) resulted in a decrease in I^2 from 73.2% to 27.8% but no substantial change in the summary odds ratio (results not shown).

In a sensitivity analysis excluding peritoneal and fallopian tube cancers, the pooled summary odds ratios for the associations between regular use of aspirin, nonaspirin NSAIDs, or acetaminophen and ovarian cancer were not substantially different from the odds ratios observed for the overall case group (data not shown). The associations between regular use of NSAIDs and ovarian cancer did not substantially change when the analyses were restricted to non-Hispanic white case patients and control subjects (data not shown). In analyses using women who reported nonregular use of all three NSAIDs as the reference group, a stronger reduced risk was observed for regular use of aspirin (OR = 0.81;

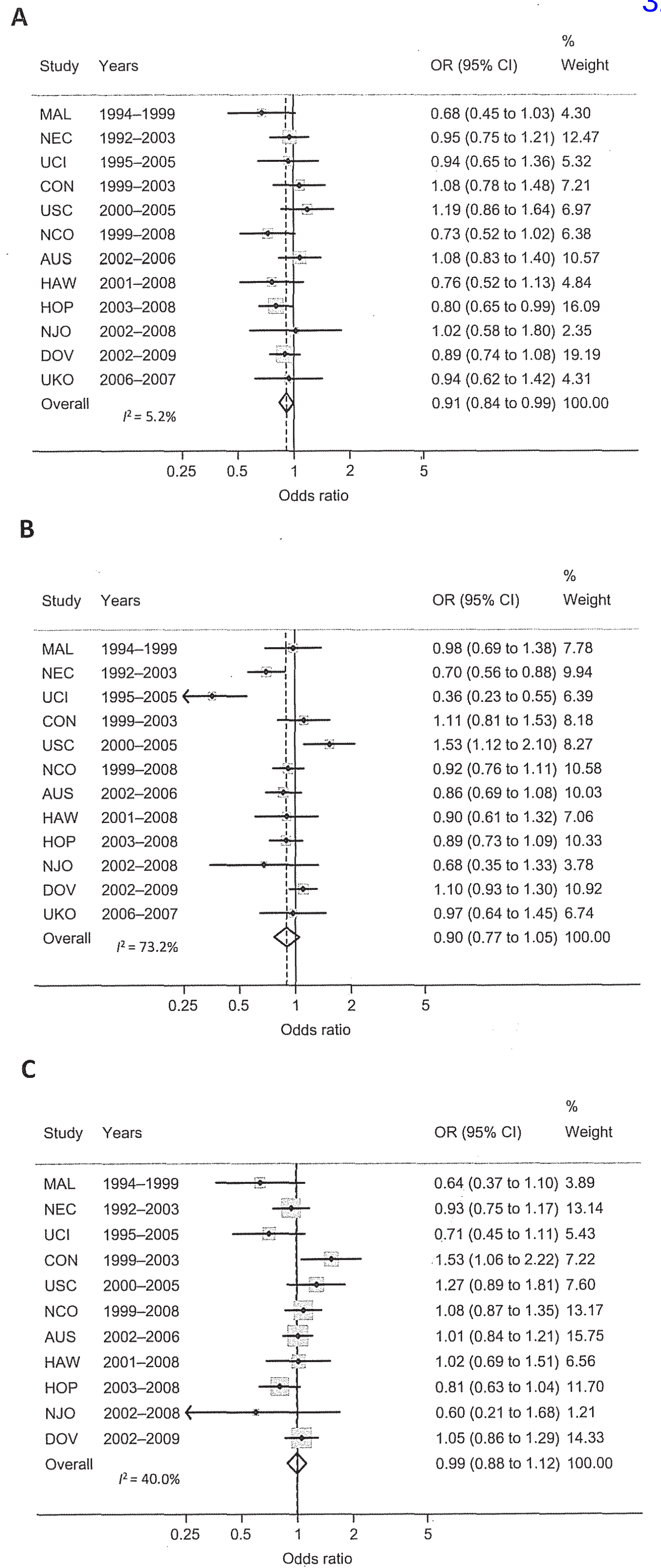

Figure 1. The summary odds ratios (ORs) and 95% confidence intervals (CIs) for the association between regular (at least once per week) use of aspirin (**A**), nonaspirin nonsteroidal anti-inflammatory drugs (NSAIDs) (**B**), and acetaminophen (**C**) and ovarian cancer risk. Summary odds ratios and 95% confidence intervals were estimated using a random-effect meta-analytic model. All statistical tests were two-sided. I^2 is the percentage of variation across studies due to heterogeneity rather than chance. % Weight describes the weight (inverse variance) each study contributed to the summary odds ratio, and the size of the surrounding **square** is an illustrative representation of study weighting. The **horizontal lines** represent study-specific confidence intervals; if ending in an **arrow**, this indicates that the interval transcends the region plotted. The **diamond** represents the summary odds ratio and 95% confidence interval. Studies are presented in order of median year of case accrual from earliest to most recent. AUS = Australian Ovarian Cancer Study, Australian Cancer Study; CON = Connecticut Ovary Study; DOV = Diseases of the Ovary and their Evaluation Study; HAW = Hawaii Ovarian Cancer Study; HOP = Hormones and Ovarian Cancer Prediction Study; MAL = Malignant Ovarian Cancer Study; NCO = North Carolina Ovarian Cancer Study; NEC = New England Case–Control Study of Ovarian Cancer; NJO = New Jersey Ovarian Cancer Study; UCI = University of California, Irvine Ovarian Cancer Study; UKO = United Kingdom Ovarian Cancer Population Study; USC = University of Southern California Study of Lifestyle and Women's Health.

95% CI = 0.68–0.99) and nonaspirin NSAID (OR = 0.86; 95% CI = 0.71–1.05), possibly reflecting reduced "contamination" of the referent group with users of NSAID types other than the medication under examination in each specific analysis (data not shown). In sensitivity analyses restricted to the six studies that specified 6 months or more as the minimum duration or the nine US studies, the pooled summary odds ratios for the associations between regular use of aspirin, nonaspirin NSAIDs, or acetaminophen and ovarian cancer were not substantially different from the odds ratios observed for the overall pooled analysis (data not shown). Finally, in the sensitivity analysis excluding case patients with the most restrictive definition of medication use, the pooled summary odds ratios for the associations between regular use of aspirin, nonaspirin NSAIDs, or acetaminophen and ovarian cancer were not substantially different from the pooled odds ratios observed for all 12 studies (data not shown).

Discussion

To our knowledge, this is the largest evaluation of aspirin, nonaspirin NSAID, and acetaminophen use and ovarian cancer risk to date. We observed a 20% risk reduction for daily users of aspirin and 34% risk reduction for regular users of low-dose aspirin. Regular (at least once per week) use of high doses of nonaspirin NSAIDs was associated with a 24% reduction in ovarian cancer risk. In contrast, acetaminophen use was not associated with ovarian cancer risk. We did not observe any substantial differences in risk by histologic subtypes of ovarian cancer.

Several established risk factors for ovarian cancer are related to inflammatory processes. During ovulation, follicles rupture and inflammatory mediators are released locally that may initiate cell transformation or that may promote growth of transformed cells (49). Proinflammatory agents are also released in inflammatory processes related to endometriosis (10). Aspirin and nonaspirin NSAIDs may reduce exposure to these inflammatory processes; thus, the reduced risk of ovarian cancer with frequent aspirin and nonaspirin NSAID use is consistent with the hypothesized inflammatory etiology of ovarian cancer (50). Several observational studies have evaluated NSAID use and the risk of ovarian cancer. (13,15,19–33,51) A recent meta-analysis reported comparable summary odds ratios for any use of aspirin (OR = 0.91; 95% CI = 0.82 to 1.01) and nonaspirin NSAIDs (OR = 0.89; 95% CI = 0.74 to 1.08), but the estimates did not reach statistical significance (51).

Table 2. Summary odds ratios (ORs) and 95% confidence intervals (CIs) for the associations of aspirin, nonaspirin NSAID, and acetaminophen/paracetamol use with risk of ovarian cancer in the Ovarian Cancer Association Consortium (1992–2009)*

Exposure	Aspirin					Nonaspirin NSAID					Acetaminophen				
categorization	Control	Case	OR†	(95% CI)	I^2‖	Control	Case	OR†	(95% CI)	I^2‖	Control	Case	OR†	(95% CI)	I^2‖
Frequency‡															
No regular use	6366	3826	1.00	(referent)		6007	3565	1.00	(referent)		6189	3497	1.00	(referent)	
<30 days per month	917	739	1.04	(0.92 to 1.18)	0.0	1357	994	1.04	(0.88 to 1.22)	44.8	1805	1439	1.10	(0.96 to 1.26)	0.0
Daily	1179	607	0.80	(0.67 to 0.96)	51.4	1285	776	0.97	(0.83 to 1.12)	46.1	665	427	0.95	(0.74 to 1.23)	63.4
Dose‡§															
No regular use	2138	1359	1.00	(referent)		2053	1274	1.00	(referent)		2465	1516	1.00	(referent)	
Low	320	129	0.66	(0.53 to 0.83)	0.0	439	259	0.96	(0.79 to 1.16)	11.7	113	68	1.15	(0.84 to 1.59)	0.0
High	415	211	0.89	(0.73 to 1.08)	0.0	490	233	0.76	(0.64 to 0.91)	0.0	500	293	0.90	(0.68 to 1.19)	60.4
Duration‡															
No regular use	6625	3667	1.00	(referent)		6451	3568	1.00	(referent)		7106	3918	1.00	(referent)	
<60 months	819	401	0.83	(0.68 to 1.01)	42.3	1002	490	0.86	(0.71 to 1.04)	48.6	477	243	0.88	(0.72 to 1.08)	26.5
≥60 months	833	527	0.98	(0.86 to 1.11)	0.0	824	525	1.08	(0.86 to 1.34)	55.6	712	438	1.13	(0.92 to 1.39)	44.4

* NSAID = nonsteroidal anti-inflammatory drug.

† Summary odds ratios were estimated using random-effects meta-analytic model. Results were adjusted for age (<50, 50–54, 55–59, 60–64, 65–69, ≥70 years), race (white, black, other), oral contraceptive use (ever/never), parity (0, 1, ≥2), menopausal status (premenopausal/postmenopausal), body mass index category (<25, 25–29.9, ≥30 kg/m^2) if available, and first-degree family history of breast cancer, male breast cancer, or ovarian cancer. All statistical tests were two-sided.

‡ Analyses included seven studies for frequency (13,23,26,37–40), three studies for dose (37,38,40), and eight studies for duration.(13,23,34,37–39,42,43).

§ Dose categories for aspirin: low: <100 mg, high: ≥100 mg; for nonaspirin NSAIDs and acetaminophen: low: <500 mg, high: ≥500 mg.

‖ I^2 is the percentage of variation across studies due to heterogeneity rather than chance.

Table 3. Summary odds ratios (ORs) and 95% confidence intervals (CIs) for the associations of aspirin and NSAID use with risk of ovarian cancer in the Ovarian Cancer Association Consortium (1992–2009)*

	Aspirin					Nonaspirin NSAID				
Exposure categorization	**Control**	**Case**	**OR†**	**(95% CI)**	**I^2§**	**Control**	**Case**	**OR†**	**(95% CI)**	**I^2§**
Frequency and dose‡										
No regular use	2138	1359	1.00	(referent)		2053	1274	1.00	(referent)	
<30 days per month, low dose	19	11	1.12	(0.52 to 2.43)	0.0	175	115	1.08	(0.74 to 1.59)	52.1
Daily, low Dose	298	118	0.64	(0.50 to 0.81)	0.0	263	143	0.88	(0.70 to 1.11)	0.0
<30 days per month, high dose	93	66	1.25	(0.88 to 1.76)	0.0	136	82	0.77	(0.57 to 1.04)	0.0
Daily, high Dose	322	144	0.78	(0.62 to 0.97)	0.0	353	148	0.75	(0.60 to 0.94)	3.8

* NSAID = nonsteroidal anti-inflammatory drug.

† Summary odds ratios were estimated using random-effects meta-analytic model. Results were adjusted for age (<50, 50–54, 55–59, 60v64, 65–69, ≥70 years), race (white, black, other), oral contraceptive use (ever/never), parity (0, 1, ≥2), menopausal status (premenopausal/postmenopausal), body mass index category (<25, 25–29.9, ≥30 kg/m²) if available, and first-degree family history of breast cancer, male breast cancer, or ovarian cancer. All statistical tests were two-sided.

‡ Analyses included three studies for frequency and dose analyses (37,38,40). Dose categories for aspirin: low: <100 mg, high: ≥100 mg; for nonaspirin NSAIDs and acetaminophen: low: <500 mg, high: ≥500 mg.

§ I^2 is the percentage of variation across studies due to heterogeneity rather than chance.

However, daily and/or low-dose aspirin use was not specifically evaluated in the meta-analysis. In contrast, the use of individual-level data in this study facilitated the evaluation of usage patterns beyond what was available in the meta-analysis of published studies.

The pharmacological effects of NSAIDs that lead to reduced risks of cancer or improved cancer prognosis are not well understood and may differ by cancer site. Aspirin is a strong, irreversible inhibitor of COX-1. Nonaspirin NSAIDs are nonselective and reversible inhibitors of both COX-1 and COX-2, whereas acetaminophen is a more effective inhibitor of COX-2 (52,53). The different effects observed in our study for aspirin/nonaspirin NSAIDs and acetaminophen may suggest that COX-1 inhibition is important for ovarian cancer risk reduction, a notion that is further supported by frequent overexpression of COX-1 in ovarian cancer tissue, but more biological and pharmacological research is needed to understand the underlying mechanisms (54).

Both epidemiologic studies and randomized trials have reported inverse associations between aspirin use and colorectal cancer, with a relative risk of approximately 0.5 for regular users (55). There is some evidence that regular and prolonged aspirin use is also associated with reduced risk of cancers of the esophagus (16), bladder (56), liver (57), lung (16), endometrium (58), and female breast (16). A recent pooled analysis of individual patient data from 51 randomized trials of aspirin use for cardiovascular disease prevention reported a 12% reduction in cancer incidence with 3 or more years of daily aspirin use (14). In women, the reduction in incidence was greatest for cancers of the female reproductive organs; however, ovarian cancer incidence was very low (14).

In the Women's Health Study, use of low-dose aspirin every other day was not associated with reduced incidence of colorectal cancer or cancer overall, suggesting that a daily use regimen is important for cancer protection (59). This notion is supported by our findings: the reduction of ovarian cancer risk was much stronger when daily use was considered, and the strongest reduction was observed among daily users of low-dose aspirin. This finding is likely explained by the regular use pattern of low-dose aspirin because low-dose aspirin regimens for cardiovascular protection are characterized by daily use over a long period of time.

Quantifying desired and adverse effects of aspirin will be important when evaluating future public health decisions about aspirin use for prevention of cardiovascular disease and cancer. Complications associated with aspirin use, including peptic ulcer, upper gastrointestinal bleeding, and hemorrhagic stroke, pose serious threats; current risk–benefit analyses favor aspirin use among high-risk groups but not for large-scale, population-based chemoprevention. Our study provides estimates on the effect of aspirin on ovarian cancer risk that should be considered in risk–benefit analyses for preventive aspirin use. However, detailed questions about frequency, dose, and duration will need to be evaluated in future studies including pooled data from cohort studies.

This pooled analysis of data from 12 studies offered several notable strengths. With more than 7500 case patients, we had greater power to detect associations than in any previous single study. Further, we were able to consistently adjust for potential confounders across studies and to evaluate NSAID exposure compared with a common reference group, reducing exposure misclassification (23). Observing consistent associations across studies and countries provided additional robustness to our findings, specifically for aspirin use, where the interstudy heterogeneity was the smallest. The use of individual-level data and the ability to consider and control for a wide range of potential confounders were additional strengths of this pooled analysis.

Potential limitations include possible differential recall of medication use between case patients and control subjects. However, the decreased risk observed for aspirin or nonaspirin NSAIDs and the lack of association with acetaminophen argues against substantial differential recall. Further, the study-specific prevalence of regular aspirin use in the US studies (11%–16%) included in the current analysis is consistent with estimates reported in US cohorts (60–62); differential recall (ie, greater reporting of medication use among case patients) would have biased our results toward the null. There was evidence of heterogeneity between study-specific estimates, but this was mostly restricted to analyses pertaining to nonaspirin NSAIDs and acetaminophen use. Nonaspirin NSAIDs include a variety of drugs and formulations with regional differences that may have contributed to heterogeneity. Another limitation of this pooled analysis was the variability in the definition of regular use across study

Table 4. Summary odds ratios (ORs) and 95% confidence intervals (CIs) for the associations of aspirin, nonaspirin NSAID, and acetaminophen/paracetamol use with risk of ovarian cancer subtype in the Ovarian Cancer Association Consortium (1992–2009)*

Subtype	Aspirin					Nonaspirin NSAID					Acetaminophen				
	Controls	Cases	OR†	(95% CI)	I^2‡	Controls	Cases	OR†	(95% CI)	I^2‡	Controls	Cases	OR†	(95% CI)	I^2‡
Serous															
No regular use	9501	3622	1.00	(referent)		8940	3467	1.00	(referent)		9326	3478	1.00	(referent)	
Use	2123	769	0.89	(0.80 to 0.99)	4.3	2754	1002	0.83	(0.68 to 1.02)	75.4	1878	777	1.03	(0.91 to 1.18)	33.3
Endometrioid															
No regular use	9460	951	1.00	(referent)		8903	858	1.00	(referent)		9264	920	1.00	(referent)	
Use	2115	183	0.90	(0.74 to 1.09)	5.5	2742	290	0.93	(0.75 to 1.15)	38.8	2277	192	0.83	(0.66 to 1.05)	29.1
Clear cell															
No regular use	8800	507	1.00	(referent)		8215	456	1.00	(referent)		9070	510	1.00	(referent)	
Use	1906	110	1.09	(0.84 to 1.41)	9.1	2561	169	0.97	(0.73 to 1.27)	35.0	3222	166	1.22	(0.91 to 1.64)	32.7
Mucinous															
No regular use	8897	308	1.00	(referent)		8340	270	1.00	(referent)		8927	314	1.00	(referent)	
Use	2312	62	0.89	(0.58 to 1.38)	38.1	2625	96	0.99	(0.73 to 1.35)	21.0	1987	66	0.90	(0.66 to 1.23)	0.0

* NSAID = nonsteroidal anti-inflammatory drug.

† Summary odds ratios were estimated using random-effects meta-analytic model. Results were adjusted for age (<50, 50–54, 55–59, 60–64, 65–69, ≥70 years), race (white, black, other), oral contraceptive use (ever/never), parity (0, 1, ≥2), menopausal status (premenopausal/postmenopausal), body mass index category (<25, 25–29.9, ≥30 kg/m²) if available, and first-degree family history of breast cancer, male breast cancer, or ovarian cancer. All statistical tests were two-sided.

‡ I^2 is the percentage of variation across studies due to heterogeneity rather than chance.

populations. We addressed the misclassification of exposure definitions across the studies by using a standard definition for regular use as described in the Methods; in the two studies with the least restrictive definition of regular use (26,37), participants were reclassified accordingly. We conducted a sensitivity analysis restricting the pooled analysis to those studies with regular use for at least 6 or more months in duration and found similar results. We were not able to reclassify participants from two studies with the most restrictive definition of regular use (23,45). In a sensitivity analysis excluding these two studies from the pooled analysis, the results were essentially unchanged. The details of NSAID use patterns ascertained in each study population differed, and data on frequency, dose, and duration of use were not provided in all studies; thus some subgroup analyses are based on small numbers. Although the point estimates for duration of use suggest a counterintuitive trend of shorter duration of use associated with lower risk of ovarian cancer, the differences were not statistically significant. It will be important to follow up the findings in large pooled prospective studies to better understand the effects of duration and timing of aspirin use and ovarian cancer risk. Further, we were not able to evaluate indication of use.

In summary, this pooled analysis supports the hypothesis that regular aspirin use reduces ovarian cancer risk. Specifically, we report a statistically significant decreased risk of ovarian cancer with daily use of aspirin. Further biological and pharmacological research is necessary to understand the mechanisms of ovarian cancer risk reduction by aspirin use.

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